REMARKS

In this Amendment, claims 1-37, 66, 67, 75, 77-79 and 83 have been amended, claims 60-65, 68-74, 80-82 and 84 have been previously presented, and claims 38-59 and 76 have been cancelled without prejudice or disclaimer. In addition, new claims 85-89 are presented herein. Accordingly, the currently pending claims are now claims 1-37, 60-75 and 77-89. It is submitted that no new matter has been added by virtue of the amended claims and the new claims, which are supported by the claims and the application disclosure as originally filed.

More specifically support for amended claim 1 is found in previous claim 31 and in the instant specification, *inter alia*, on page 35, lines 3-12, and on page 49, Example 2, lines 5-8. Support for amended claim 4 is found in the instant specification, *inter alia*, on page 24, lines 3-11. Additionally, claims 2, 3, 5-30, 32-37, 66, 67, 75, 77-79 and 83 have been amended to correct clerical oversights and/or to clarify the claim language. New claims 85-87 are supported by prior claim 6; new claim 88 is supported by prior claim 17; and new claim 89 is supported by the instant specification, *inter alia,* on page 42, lines 19-22 and Examples 1-4, pages 48-50.

The claims fulfill the requirements of 35 U.S.C. §112, second paragraph

Claim 4 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. According to the Examiner, the term "reversibly solidified active substance" renders claim 4 indefinite "because it is not clear what compounds or active substance are considered "reversibly solidified". In response, claim 4 has been amended, based upon the instant disclosure, to clarify the claim language, thereby obviating alleged indefiniteness. Withdrawal of the rejection is thus respectfully requested.

Double Patenting

Claims 1-37 and 60-84 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-19 of U.S. Patent No. 6,616,949 ('949) and over claims 1-19 of U.S. Patent No. 6,706,288 ('288). According to the Examiner, the conflicting claims are not identical to the '949 and the '288 patents, respectively, but are considered not patentably distinct from each other.

Applicants respectfully request that this rejection be held in abeyance until the claims in the instant application have been deemed to be allowable, at which time, Applicants will file one or more appropriate terminal disclaimers.

The claims fulfill the requirements of 35 U.S.C. § 103(a)

Claims 1-37 and 60-84 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Woiszwillo et al. (U.S. Patent No. 5,981,719), hereinafter "Woiszwillo", and Ekman et al. (U.S. Patent No. 4,822,535), hereinafter "Ekman", in view of Laakso et al. (*J. Pharm. Sci.*, 1986, 75(10):962-967, hereinafter "Laakso", and Takada et al. (U.S. Patent No. 5,622,657), hereinafter "Takada". The Examiner states that the references do not expressly teach the method of preparing microparticles by employing the method of Woiszwillo followed by that of Ekman. However, the Examiner opines that it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the "herein claimed microparticles" by employing the method of Woiszwillo followed by that of Ekman. According to the Examiner, one of ordinary skill would have been motivated to do so because "Woiszwillo's method is to prepare a microparticle and then Ekman et al. would further encapsulate such microparticle to increasing [*sic*] the stability of the biological [*sic*] active substances."

It is respectfully submitted that Applicants' presently-claimed invention, considered in its entirety, is not obvious in view of Woiszwillo and Ekman, either alone, in combination, and/or in combination with Laakso and Takada, as the invention is directed to a novel method of preparing microparticles containing a biologically active substance, which is not taught, suggested, or contemplated by the cited references.

It is Applicants who provide a distinct and new method of producing parenterally administrable microparticles that contain a biologically active substance. Applicants' method involves the formation of a concentrated biologically active substance, e.g., a concentrated solution or a solid particle precipitate of the biologically active substance, when mixed with polyethylene glycol. The concentrated biologically active substance is mixed with starch

solution prior to solidification into microparticles. See, e.g., page 20, lines 8-11 of the instant application, (paragraphs [0046]-[0052] of the published application no. US 2002/0081336 A1).

Applicants' invention provides a process to produce microparticles in which a biologically active substance is stabilized in the microparticles. Because the biologically active substance is in a concentrated form during the practice of Applicants' method, the biologically active substance does not distribute out into the outer phase during microparticle preparation, as described on page 21, lines 4-6 of the instant application, (paragraph [0055] of the published application no. US 2002/0081336 A1). Neither Woiszwillo nor Ekman, alone or combined, teaches or discloses Applicants' invention considered in its entirety. In addition, neither Woiszwillo nor Ekman, alone or combined, contains teaching or disclosure that would lead one having skill in the art to make the modifications necessary to arrive at Applicants' claimed invention. Consequently, the claimed invention is not made obvious by the cited art, alone or in combination.

The cited art describes distinct and complete methods of producing microparticles. While Woiszwillo discloses a simple, single-phase, aqueous-based method, Ekman discloses a more complex, multi-phase, emulsion-based method. The methods of Woiszwillo and Ekman are different from each other, and are distinct from the presently claimed invention. That these methods produce microparticles as an end product is irrelevant, since Applicants' claimed invention is directed to a method or process of making microparticles. As such, Applicants' claimed method comprises steps that, when considered in their entirety, are distinct from the methods and systems disclosed in the cited art references. In this regard, Applicants respectfully submit that it is the steps of the processes or methods that should be considered in their entirety, and not the microparticles as an end product of the methods, in a determination of patentability under 35 U.S.C. § 103(a).

Applicants respectfully disagree that using Woiszwillo's system as one of the immiscible systems and applying it to Ekman's system would seem to be "reasonable and obvious" to the ordinarily skilled artisan, as opined by the Examiner (06/22/2004 Office Action, page 11), because Woiszwillo's method/system is described as a simple, single-phase process that particularly avoids emulsion systems that are not miscible with water. It would detract from the

simplicity and rapidity of Woiszwillo's method if it were used as a phase in the multi-phase emulsion system of Ekman. Indeed, the methods of Woiszwillo and Ekman constitute distinguishable microparticle-preparation systems in the art. The present invention is not made obvious by a combination of Woiszwillo and Ekman, since there is no logical or reasonable motivation, either in the references or in the art, to combine the teachings of these references.

It is also respectfully submitted that neither Laakso, (which teaches that polyacryl starch may be used as a carrier for passive target drug delivery), nor Takada, (which teaches a sustained release formulation biologically active microparticles coated by copolymers of polylactic/glycolic acid), make up for the deficiencies of the primary and secondary references and thus do not render the presently claimed invention obvious, alone or in combination.

Applicants respectfully disagree that one skilled in the art would have been motivated to combine the teaching of Woiszwillo with the teaching of Ekman to "further encapsulate" the microparticles prepared by Woiszwillo's method so as to increase stability of the biologically active substances.

Woiszwillo discloses and teaches a complete method of making microparticles in a single-phase aqueous system in the absence of any non-aqueous phase. In fact, it is a stated object of Woiszwillo **not** to utilize a multi-phase, water-in-oil emulsion during the manufacture of the microparticles. In this regard, Woiszwillo specifically discloses that:

> [i]t is a further object of the present invention to provide a process for making microparticles that uses only aqueous or aqueous miscible solvents and does not utilize a water-in-oil emulsion in the manufacturing of the microparticles. (Col. 4, lines 21-24, emphasis added).

The above-cited disclosure is a plain teaching that Woiszwillo's method would not be part of, or combined with, a multi-phase method utilizing emulsions involving water and oil, such as that of Ekman. Woiszwillo teaches as the object of the disclosed invention a relatively simple, rapid and inexpensive single-phase process for making microparticles (Col. 4, lines 17-

19), in which the process is to be carried out using water or water miscible solvents in the absence of an emulsion.

This is a clear teaching away from a combination with Ekman, which teaches and encompasses a multi-phase system involving immiscible phases and emulsions. Therefore, one having skill in the art would not be driven to combine Woiszwillo with Ekman, because it would be not only counterintuitive, but also unnecessary, in view of an understanding of Woiszwillo's complete method and Ekman's complete method. Indeed, Woiszwillo's complete method leads to the production of microparticles containing biological substances that can be stabilized without a need or an impetus by the skilled artisan to perform more complicated or additional encapsulation steps involving non-aqueous phases.

Applicants also respectfully disagree that one of skill in the relevant art would be motivated to combine two, completely disparate methods that comprise different steps, and that yield stabilized microparticles in their own ways, based mainly on a desire to increase stability, as asserted by the Examiner. (06/22/04 Office Action, page 10). Applicants point out that Woiszwillo specifically addresses the stabilization of microparticles prepared according to Woiszwillo's method. Indeed, as taught by Woiszwillo: "[t]he microparticles may also be coated with one or more stabilizing substances, which may be particularly useful for long term depoting with parenteral administration or for oral delivery ...". (Col. 10, lines 37-40). Woiszwillo further discloses that the microparticles can be stabilized with a coating of mucin, for example, (Col. 10, lines 43-46), or alternatively, they can be coated with compounds such as fatty acids or lipids. According to Woiszwillo, "the coating may be applied to the microparticles by immersion in the solubilized coating substance, spraying the microparticles with the substance, or other methods known to those skilled in the art." (Col. 10, lines 47-52).

Thus, Woiszwillo plainly teaches ways of coating and/or stabilizing the microparticles prepared using Woiszwillo's single-phase method so that one having skill in the art is not motivated to include or to perform (an) additional encapsulation step(s) involving non-aqueous emulsion techniques, as taught by Ekman. (Col. 8 of the '535 patent).

In addition, Woiszwillo's method is stated to be relatively simple and rapid, such that it involves a single phase, comprising mixing macromolecules in aqueous solution, (or liquid phase), with a polymer or a polymer mixture in solution, (or liquid phase), in the presence of an energy source, (e.g., heat), for a time sufficient to form microparticles, for example, by removal of water from the macromolecules. (See, Col. 7, lines 5-14). The so-formed microparticles are then separated from unincorporated components in the solution and can be stabilized as also taught by Woiszwillo. (See, Col. 7, lines 36-39 and Col. 10, lines 37-52).

Unlike Ekman, Woiszwillo plainly teaches an essentially simple, one-phase system comprising a solution mixture of macromolecules and polymer(s) that form following exposure of the solution to an energy source. This system yields microparticles without having or needing to combine two immiscible solutions to form microparticles via a dispersion or emulsion, as does Ekman. Each of the methods of Woiszwillo and Ekman generates microparticles in its own way, and each of the methods of Woiszwillo and Ekman provides a means for stabilizing the microparticles, particularly those containing macromolecules.

Considering the above, it is respectfully submitted that Woiszwillo contains teaching that does not lead the skilled practitioner toward a multi-phase system, in which the solution for the dispersed phase is added to another solution to form a dispersion, such as taught by Ekman at Col. 6, lines 41-44.

In short, Ekman's disclosed method embraces a multi-phase system, which is "characterized by using two mutually immiscible aqueous phases as the liquid phases". (Col. 1, lines 56-59), while Woiszwillo's disclosed method embraces only aqueous miscible solvents in one simple phase, as discussed above. Both of the methods of Woiszwillo and Ekman comprise distinct steps and lead to microparticles containing biological substances that can be stabilized according to the specific teachings of each of the two respective references, without a need or contemplation of combining with another method of microparticle production. Accordingly, there is no reasonable impetus, motivation, or incentive provided to the ordinarily skilled person in the art to combine Woiszwillo's complete, single-phase method/system with Ekman's complete, multi-phase method/system to further encapsulate a biological substance to increase stability. Moreover, as discussed above, the steps of Applicants' claimed method, considered in

their entirety, are distinct and non-obvious in view of the complete disclosures of Woiszwillo and Ekman, considered in their entireties, taken alone or in combination.

In view of the foregoing discussion and explanation, it is respectfully requested that the rejection under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

Applicants respectfully submit that the application is now in condition for allowance. An action progressing this application to issue is courteously urged.

Should any additional fees be deemed to be properly assessable in this application for the timely consideration of this Amendment, or during the pendancy of this application, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. **50-0311** (Reference no. 28069-594).

Should an Extension of Time be required in connection with the filing of this Amendment, the Commissioner is hereby requested to grant any such Extension of Time as may be deemed necessary, and is authorized to charge any such Extension of Time Fee as may be required to keep the application in good standing, to Deposit Account No. **50-0311** (Reference no. 28069-594).

If the Examiner is of the opinion that further discussion of the application would be helpful, the Examiner is hereby respectfully requested to telephone the applicants' undersigned representative at (212) 692-6742 and is assured of full cooperation in an effort to advance the prosecution of the instant application and claims to allowance.

Respectfully submitted,
MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C.

Date: September 22, 2004

By: Leslie A. Serunian
Leslie A. Serunian
Registration No. 35,353

Correspondence Address:
MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
Chrysler Center
666 Third Avenue
New York, New York 10017
Telephone: (212) 935-3000
Facsimile: (212) 983-3115
Direct Tel.: (212) 692-6742